Exogenous sex steroid hormones and asthma in females: protocol for a population-based retrospective cohort study using primary care data

Bright I Nwaru,[1,2] Colin R Simpson,[1] Ireneous N Soyiri,[1] Rebecca Pillinger,[1] Francis Appiagyei,[3] Dermot Ryan,[3] Hilary Critchley,[4] David Price,[3] Catherine M Hawrylowicz,[5] Aziz Sheikh[1]

[1]Asthma UK Centre for Applied Research, Centre for Medical Informatics, Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, Edinburgh, UK
[2]School of Health Sciences, University of Tampere, Tampere, Finland
[3]Optimum Patient Care, The Old Granary, Cambridge, UK
[4]Medical Research Council Centre for Reproductive Health, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK
[5]MRC-Asthma UK Centre in Allergic Mechanisms of Asthma, Division of Asthma, Allergy and Lung Biology, Guys Hospital, Kings College, London, UK

Correspondence to:
Bright Nwaru
Usher Institute of Population Health Sciences and Informatics
University of Edinburgh
Old Medical School
Teviot Place, Edinburgh EH8 9AG, UK
Email: bright.nwaru@ed.ac.uk

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ABSTRACT

Introduction: Female sex steroid hormones have been implicated in the sex-related differences in the development of clinical outcomes of asthma. The role of exogenous sex steroids however remains unclear. Our recent systematic review highlighted the lack of high quality population-based studies investigating this topic. We aim to investigate whether the use of hormonal contraceptives and hormone replacement therapy (HRT) and their subtypes is associated with risk of developing clinical outcomes from asthma in reproductive age and menopausal/postmenopausal females.

Methods and analysis: Using the Optimum Patient Care Research Database (OPCRD), a national primary care database in the UK, we will construct a retrospective longitudinal cohort of reproductive age (16-44 years) and menopausal/postmenopausal (45-70 years) females. With 90% power, we need 23,700 reproductive age females to detect up 20% reduction (risk ratio 0.8) in asthma exacerbations for use of any hormonal contraceptives and 6000 menopausal/postmenopausal females to detect up to 40% (risk ratio 1.40) increased risk of asthma exacerbation for use of any HRT. The OPCRD has at least 700,000 16-70-year females that will meet our inclusion criteria. We will estimate the risk of new-onset asthma given prior exposures to sex steroids using Cox regression or generalised linear models if specific time of asthma onset is uncertain. Generalised estimating equations (GEE) will be used to study the associations between sex steroids and repeated asthma outcomes, such as exacerbations and hospitalisations. We will adjust for confounding factors in all analyses. We will evaluate interactions between the sex hormones and body mass index, smoking and alcohol use by calculating the relative excess risk due to interaction and the attributable proportion due to interaction.

Ethics and dissemination: As only anonymised non-identifiable data are used, self-audited assessment of the University of Edinburgh indicated no further ethics approval are required to undertake this piece of work. Optimum Patient Care has a subsisting NHS ethics approval for the use of the OPCRD data for research (15/EM/150). We will apply to the Anonymised Data Ethics Protocols and Transparency (ADEPT) Committee, which grants project-specific approvals for the use of the OPCRD data. We will present our findings at national and international scientific meetings and publish the results in international peer-reviewed journals.

Protocol registration: We will register the study protocol with Clinicaltrial.gov prior to starting the analyses.

INTRODUCTION

Asthma is more common in boys than girls during early childhood, but the prevalence and severity are higher in females than males after puberty.[1-3] Female sex steroid hormones are believed, at least in part, to explain these sex-related variations in asthma outcomes.[1-3] Variations in asthma incidence and clinical outcomes are seen to follow the hormonal transitional points in the female's reproductive cycle, such as pregnancy, puberty, menarche, menstruation and menopause.[1,4] Fluctuations of oestradiol and progesterone levels during the menstrual cycle have been linked to worsening of asthma symptoms in females.[5] A predominance of T-helper (Th) cell 2 over Th cell 1-mediated immunity has also been observed during the premenstrual period.[6,7] Both oestrogen and progesterone influence smooth muscle functions, inflammation, and airway responsiveness.[6,7] A recent observation showed that in patients with severe asthma, both oestrogen and progesterone were associated with decrease in the expression of the left-7f microRNA as well as an increase in IL-23/IL-23 receptor signalling and IL-17A production.[8] Some evidence suggest that external suppression of endogenous sex steroid production through the use of exogenous hormonal contraceptives may improve asthma outcomes,[9-13] whereas the use of hormone replacement therapy (HRT) by menopausal women to enhance production of endogenous sex steroids may increase the risk of new onset asthma as well as risk of poor clinical outcomes.[14-19] Females with asthma appear to exhibit reduced Th2 responses, reduced asthma symptoms, and improved lung function when taking hormonal contraceptives.[5,7,20,21]

Using the serial cross-sectional Scottish Health Surveys, we recently observed substantial reductions in asthma exacerbations and hospital episodes in females using hormonal contraceptives compared to those not using hormonal contraceptives.[12] This work was followed by a comprehensive synthesis of the underlying evidence, which revealed inherent methodological limitations in previous studies on the topic, including paucity of prospective longitudinal studies and limitations in measurement of sex steroids and asthma outcomes.[22] To overcome these weaknesses and thus clarify whether the role of sex steroid hormones in asthma in females is putatively causal, well-designed long-term longitudinal studies with well-characterised populations are required. Therefore, we plan to create a retrospective longitudinal cohort of reproductive age and menopausal/postmenopausal females using the Optimum Patient Care Research Database (OPCRD) in order to investigate the role of exogenous sex steroid hormones in clinical and patient-reported asthma outcomes in females. Specifically, we aim to investigate the:

1. Associations between use of hormonal contraceptives and sub-types (oestrogen, progesterone) and asthma exacerbations, hospitalisation, severity, mortality and health-related quality of life (HRQoL) in reproductive age females.
2. Associations between use of HRT and sub-types (oestrogen, progesterone) and asthma exacerbations, hospitalisation, severity, mortality and HRQoL in menopausal/post-menopausal females.
3. Interactions between exogenous sex hormones, body mass index (BMI), cigarette smoking and alcohol in these associations.

METHODS

Ethics approvals and permissions

The main ethical issues relate to anonymity, confidentiality, data protection and the linkage of datasets. We processed the Level 1 self-audit ethics forms the Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh; this self-audit indicated that no further ethical permissions were required as the project involves the use of anonymised data. Optimum Patient Care has a subsisting NHS ethics approval for the use of the OPCRD for research (15/EM/150). However, project-specific approvals are granted by the Anonymised Data Ethics Protocols and Transparency (ADEPT) Committee, which has been commissioned by the Respiratory Effectiveness Group. We will apply and obtain the ADEPT approvals prior

to commencing data extractions and analyses. All researchers involved in the analysis will have successfully completed the Scottish Health Informatics Programme Information Governance course or equivalent.

Study design and population

The OPCRD database is a bespoke longitudinal anonymised primary care database representing over 570 general practices across the UK and is regularly used to conduct epidemiological, clinical, and pharmaceutical research (www. http://optimumpatientcare.org/opcrd/).. A major advantage of the OPCRD database is the focus on respiratory outcomes; in addition, for up to 10% of patients in the database with asthma, patient-reported questionnaire data on asthma outcomes are also available. This provides the opportunity to study both clinical and patient-reported outcomes from the database. The study population for the present investigation will comprise of all 16-70 year-old females in the OPCRD database. We will construct two independent cohorts to address the study objectives, namely:

1. Reproductive age females (16-44 years old) to study the associations between use of hormonal contraceptives and the study outcomes
2. Menopausal/post-menopausal females (45-70 years old) to study the associations between HRT and the study outcomes.

Exposures

We will ascertain the use of hormonal contraceptives and HRT by means of the Read Clinical Classification System (Read codes).[23,24] We will define the following exposures: use of hormonal contraceptives and HRT, their subtypes (oestrogen-only, progesterone-only, and combined therapy), frequency and duration of their use.

Confounders

Potential confounders will be extracted from the database using their respective Read codes, including age, parity, ethnicity, BMI, smoking, alcohol intake, current use of asthma treatments and level of adherence to these, Index of Multiple Deprivation,[25] and co-morbidity based on the Charlson index.[26]

Outcomes

The primary outcomes will include new-onset asthma, asthma exacerbations and hospitalisations. New-onset asthma will be defined as the first GP-recorded asthma event (including diagnosis, hospitalisation, medication prescription, or any other asthma event) occurring at least five years from the follow-up date. We will exclude individuals with a relevant primary care diagnosis of asthma recorded up to five years prior to the index episode. Asthma exacerbations and hospitalisations will be defined based on the frequency of GP consultation, oral steroid courses and hospital admissions for asthma, respectively. The outcomes will be determined using relevant Read codes. The secondary outcomes will include patient-reported asthma symptoms, medication use, and HRQoL.

Follow-up period

We will follow the participants from baseline starting from 1 January 2000 until 31 December 2016 in order to observe subsequent occurrence of the study outcomes. Exit date from the cohort will be defined as the date of first diagnosis of asthma (i.e. date of first record of an asthma encounter), death, deregistration from a practice, or end of follow-up (31 December 2016), whichever comes first.

Statistical analyses

Prior to the main analyses, the data will undergo relevant quality checks, including relevant variable categorisation, re-scaling where appropriate, and checks for missingness. We will undertake complete case analysis and perform multiple imputation for variables with missing

values. We will perform 20 imputations in order to enhance the efficiency of the estimates and will use Rubin's rule to combine the estimates across the 20 datasets.[27] Where the specific time of onset of asthma is observable, we will perform survival analysis using the log-rank test to describe the survival functions of the groups as defined by use of sex hormones and Cox proportional hazards regression to study the associations between exogenous sex hormones and the first record of an asthma event. If the specific time for new-onset asthma is unobservable, we will use generalised linear model to estimate the relative risk of asthma occurrence given prior exposure to sex steroid hormones. Generalised estimating equations (GEE) will be used to estimate associations where the outcomes are repeated, e.g. number of asthma exacerbations, medication use, and hospitalisations. We will undertake analyses incorporating propensity scores using matching (exposed vs. unexposed).[28] The model will be non-parsimonious in order to include a wide range of factors that influence propensity to be prescribed hormonal contraceptives and HRT. To minimise potential biases, we will undertake different scenarios of sensitivity analyses in order to evaluate the robustness of our findings, including analyses for potential selection bias at baseline, unmeasured confounding, and information bias.[29] These sets of bias analyses will be aided by deriving relevant internal data from a subset of the study population where possible or obtain external validation data that will provide the basis for defining the sensitivities of the different measures and allow appropriate adjustments to be made to our estimates. We will also evaluate potential of confounding by indication bias by stratifying the analyses by relevant disease indication for using sex steroid preparations. To estimate the potential interactions between sex hormones and BMI, cigarette smoking, and alcohol, we will calculate the relative excess risk due to interaction and the attributable proportion due to interaction.[30] All estimates will be accompanied by their respective 95% confidence intervals. Statistical analyses will be undertaken using STATA 14 statistical software.

Sample size estimation

Given estimates of our previous exploratory analysis using the Scottish Health Surveys (31% using any hormonal contraceptives, 6.5% with physician-diagnosed asthma, and an odds ratio of 0.68, 95% confidence interval 0.47-0.98),[12] we determined that in order to have 90% power at an alpha level of 0.05 to detect up 20% reduction (risk ratio 0.8) in asthma exacerbations, we will need a sample size of 23700 reproductive age females given use of any hormonal contraceptives. Furthermore, with 90% power at an alpha level of 0.05, we determined that we will need 6000 menopausal/postmenopausal females to detect up to 40% (risk ratio 1.40) increased risk of asthma exacerbation for use of any hormone replacement therapy.[19]

Timelines and milestones

Timeline	**Milestone**
April – August 2017	• Protocol development, registration and publication • Permissions and ethics approvals
August – December 2017	• Data acquisition • Data processing and cleaning • Preliminary data analyses
January – May 2018	• Data analyses completed
May – October 2018	• Prepare project report • Conference abstracts and scientific papers

Dissemination plans

The project findings will be presented in national and international scientific meetings and published in international journals. Furthermore, we will capitalise on the dissemination infrastructure of the Asthma UK Centre for Applied Research (e.g. the Twitter feed and dynamic website) to publicise our findings to clinicians, academics and patients, and to develop follow-on major grant applications to UK-wide funders.

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Conflict of interests
The authors declare no conflicting of interest related to this work.

Contributorship
BN and AS conceived the idea for this work. It was drafted by BN and was then revised after several rounds of critical comments from CRS, CMH, and AS and additional feedback from INS, RP, HC, FA, DR, and DP.

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